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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/066,021	01/31/2002	Richard Leslie Edelson	270425.0008	4728

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EXAMINER	
NGUYEN, QUANG	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 12/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/066,021	EDELSON ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *16-21 and 23-25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5/29/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 1-25 are pending in the present application.

Applicant's election with traverse of Group I (claims 1-15 and 22) in the Response to Restriction requirement dated 9/3/03 is acknowledged. The traversal is on the ground(s) that a search of the entire application can be made without serious burden because a thorough search for the subject matter of Group I would overlap with a search for the subject matter of Group II. This is not found persuasive because the methods of Groups I-II have different starting materials, different method steps, different technical considerations for achieving the desired end-results and that they each can be carried out independently one from the other. For example, unlike the methods of Group I, the method of Group II requires the specific step of coating disease effector agents in the extracorporeal quantity of blood with monoclonal antibodies having a free Fc segment. This would require a separate search requirement, and therefore it would be unduly burdensome for the examiner to search and/or consider the patentability of both the inventions within a single application.

The requirement is still deemed proper and is therefore made FINAL.

Claims 16-21 and 23-25 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the Response to Restriction requirement dated 9/3/03.

Accordingly, claims 1-15 and 22 are examined on the merits herein.

Claim Objections

Claims 1, 2, 9, 13 and 22 are objected to because the phrase "the the extracorporeal quantity of blood" is grammatically incorrect. Appropriate correction is required.

Claim 9 is further objected to because of the term "5mm". A space should be inserted between 5 and the unit mm. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 6-12, 14-15 and 22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

(1) A method for producing functional antigen presenting dendritic cells from an extracorporeal quantity of a subject's blood, said method comprising the steps of:

(a) treating the extracorporeal quantity of blood with a photoactivatable agent capable of inducing apoptosis in disease effector agents contained in the flood;

(b) subjecting the extracorporeal quantity of blood to a leukapheresis process;

(c) flowing the extracorporeal quantity of blood from step (b) through a photopheresis apparatus having plastic channels with a diameter of about 1 mm or less;

(d) irradiating the extracorporeal quantity of blood from step (c) as it flows through the photopheresis apparatus; and

(e) incubating the extracorporeal quantity of blood after treatment in the photospheresis, whereby functional antigen presenting dendritic cells are produced from monocytes containing in the extracorporal quantity of blood;

(2) A method for producing functional antigen presenting dendritic cells from an extracorporeal quantity of a subject's blood, said method comprising the steps of:

(a) inducing apoptosis of disease effector agents contained in the extracorporeal quantity of blood;

(b) subjecting the extracorporeal quantity of blood to a leukapheresis process;

(c) flowing the extracorporeal quantity of blood from step (b) through plastic channels having a diameter of between about 0.5 mm and about 5 mm; and

(d) incubating the extracorporeal quantity of blood following passage through the plastic channel, whereby functional antigen presenting dendritic cells are produced from monocytes containing in the extracorporal quantity of blood;

(3) A method for producing functional antigen presenting dendritic cells from an extracorporeal quantity of a subject's blood, said method comprising the steps of:

(a) inducing apoptosis of disease effector agents isolated from the subject;

(b) subjecting the extracorporeal quantity of blood to a leukapheresis process;

(c) flowing the extracorporeal quantity of blood from step (b) through plastic channels having a diameter of about 1 mm or less;

(d) combining the apoptotic disease effector agents with the extracorporeal quantity of blood from step (c); and

(e) incubating the combined apoptotic disease effector agents and the treated blood from step (c), whereby functional antigen presenting dendritic cells are produced from monocytes containing in the extracorporal quantity of blood;

does not reasonably provide enablement methods of producing a functional antigen presenting dendritic cells from any cell population containing in an extracorporeal quantity of a subject's blood, and in the absence step (b) above. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

The specification teaches by exemplification showing the enhanced photopheresis protocol (including the leukapheresis step) of the present application resulted in large numbers of mature dendritic cells derived from monocytes and

apoptotic T cells in blood samples subjected to photopheresis and incubation for about 22 hours. Applicants also teach that the centrifugal forces associated with leukapheresis together with an overnight incubation are also sufficient to induce efficiently a large number of mature dendritic cells from isolating monocytes. Without subjecting to photopheresis, little apoptosis of T cells was observed in the T cell population isolated by leukapheresis. The specification also discloses that a treatment method based on the enhanced photopheresis protocol of the presently claimed invention has been tested in a pilot study involving four cutaneous T-cell lymphoma (CTCL) subjects whose disease had been advancing while on standard photopheresis. Over a twelve-month treatment period, although no subject experienced complete hematologic remissions, previous rapid increases in blood CTCL cells were reversed. There was also a lack of symptomatic infections common in individuals whose immune systems have been compromised by their CTCL as well as a decrease in the severity and distribution of skin lesions in treated subjects. The evidence has been noted and considered. However, the evidence is not reasonably extrapolated to the instant broadly claimed invention for the following reasons.

(1) The breadth of the claims. The instant claims encompass a method for producing functional antigen presenting denderitic cells from an extracorporeal quantity of a subject's blood without the requirement of a leukapheresis step, simply flowing an extracorporeal quantity of blood through plastic channels, including those in a photopheresis apparatus, having the recited diameters (e.g., about 1 mm or less or between about 0.5 mm and about 5 mm), and that functional antigen presenting

dendritic cells are produced from any cell population containing in the extracorporeal quantity of blood.

(2) The state and the unpredictability of the art. At about the effective filing date of the present application, nothing was known on the process of producing functional antigen presenting dendritic cells from an extracorporeal quantity of a subject's blood simply by flowing the extracorporeal quantity of blood through plastic channels, including those in a photopheresis apparatus, of certain diameters. Additionally, the physiological art is recognized as unpredictable (MPEP 2164.03), particularly for the process of differentiation and/or producing functional antigen presenting cells from any cell population in an extracorporeal quantity of a subject's blood.

(3) The amount of direction or guidance presented. Apart from disclosing that irradiation of the monocytes with a photoactivable agent during the photophoresis process (including the leukapheresis step) or subjecting the monocytes to centrifugal forces associated with leukapheresis, followed by an effective incubation period (see Fig. 1) resulted in the generation of a large number of mature dendritic cells, the instant specification offers no guidance for a skilled artisan in the art on how to induce the differentiation of monocytes or any cell population present in an extracorporeal quantity of a subject's blood (including monocyte-depleted blood) into functional dendritic antigen presenting cells, simply flowing an extracorporeal quantity of blood through plastic channels of certain diameters. Although Applicants hypothesized the fluid flow through the plastic channel walls of a photopheresis apparatus imposes shearing forces

on the adhered monocytes to cause the monocytes to detach, and several episodes of adherence and detachment from the plastic channel walls during the photopheresis process resulted in the differentiation of monocytes into functional dendritic cells, there is no evidence of record indicating that the passage of an extracorporeal quantity of a subject's blood alone (without treating the blood to a leukapheresis step) is sufficient for inducing the differentiation of monocytes to functional dendritic cells. Nor is there any evidence of record indicating that any cell population present in an extracorporeal quantity of a subject's blood is capable of being induced to generate functional dendritic cells by the methods as claimed. Based on the present disclosure, it is apparent that the critical features of the presently claimed invention are the leukapheresis step and the co-cultivation or incubation step of the generated antigen presenting dendritic cells from treated monocytes contained in an extracorporeal blood with treated disease effector cells. Therefore, such critical elements or features must be present in the claims. Since the prior art at the effective filing date of the present application does not provide guidance for the methods as claimed, it is incumbent upon the present application to do so. With the lack of sufficient guidance provided by the present specification, it would have required undue experimentation for one skilled in the art to make and use the instant broadly claimed invention.

As set forth in *In re Fisher*, 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> That scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the are; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions

> and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

The Appeal courts have also stated that reasonable correlation must exist between scope of exclusive right to patent application and scope of enablement set forth in the patent application (27 USPQ2d 1662 *Ex parte Maizel.*).

Accordingly, due to the lack of sufficient guidance provided by the specification regarding to the issues set forth above, the unpredictability of the physiological art, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to make and use the instant broadly claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-15 and 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 1, 9, their dependent claims and claim 22, there is no connection between the recited steps with "producing functional antigen presenting dendritic cells from an extracorporeal quantity of a subject's blood" in the preamble of the claims. Clarification is requested because the metes and bounds of the claims are not clearly determined.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1, 6-8 and 9-15 are rejected under 35 U.S.C. 102(a) as being anticipated by Berger et al. (Journal of Investigative Dermatology 112 (4), April 1999, page 580, Abstract 345) as evidenced by Edelson (U.S. Patent No. 4,683,889; IDS).

Berger et al. disclose a method comprising subjecting leukocytes from cutaneous T cell lymphoma (CTCL) patients to an extracorporeal photopheresis (ECP) procedure, and **following a 20 h incubation step** monocytes obtained from ECP-treated CTCL patients exhibit dendritic antigen presenting cells (DAPC) phenotypic and functional properties, whereas monocytes obtained from untreated CTCL patients did not express elevated levels of DAPC markers (see the abstract). Berger et al. further teach that in contrast to lymphocytes, which undergo apoptotic cell death after exposure to 8-methoxypsoralen and ultraviolet A light, monocytes not only survive but become activated. The ECP procedure taught by Berger et al. also comprises the steps of treating an extracorporeal quantity of blood with a photoactivatable agent capable of inducing apoptosis in disease effector agents contained in the blood, flowing the extracorporeal quantity of blood through a photopheresis apparatus having plastic channels having a diameter within the recited limitation as evidenced by the teachings of Edelson (see abstract Figure 1, and particularly col. 13, lines 45-50 and the claims).

Since the irradiation chamber has a thickness in the range of from about 0.05 to 10 mm, the plastic channels within the irradiation chamber must also have a diameter within the recited range. Edelson further teaches that the ECP procedure also involves a step in which a centriguge can be used prior to exposure of the blood to radiation to isolate a blood fraction enriched in red blood cells and a fraction enriched in lymphocytes and other nucleated leukocytes, while the red blood cells may be immediately returned to the subject along with most of the blood plasma while the concentrated lymphocyte fraction is diluted and delivered to the irradiation source (col. 10, lines 42-53).

Accordingly, Berger et al. anticipate the instant claimed invention.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-15 and 22 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-16 of U.S. Patent No. 6,607,722. Although the conflicting claims are not identical, they are not

patentably distinct from each other because a method of enhancing the presentation of disease associated antigens in the issued U.S. Patent No. 6,607,722 (e.g., comprising the steps of treating monocytes contained in an extracorporeal quantity of a mammal's blood which had been subjected to a leukapheresis process by pumping the monocytes through a plastic channel in a photophoresis apparatus, having a diameter of about 1 mm, and incubating the treated monocytes with treated disease effector agents for a period of time sufficient to induce induce differentiation of the monocytes into functional dendritic antigen presenting cells) which is a species or sub-genus anticipates the claimed genus in the application being examined and, therefore, a patent to a genus would, necessarily, extend the rights of the species or sub-genus should the genus issue as a patent after the species or subgenus.

Claim 22 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 6,524,855. Although the conflicting claims are not identical, they are not patentably distinct from each other because a method for inducing differentiation of monocytes contained in an extracorporeal quantity of a mammal's blood into functional dendritic antigen presenting cells in the issued U.S. Patent No. 6,524,855 (e.g., comprising the steps of treating monocytes contained in an extracorporeal quantity of a mammal's blood which had been subjected to a leukapheresis process by pumping the monocytes through a plastic channel in a photophoresis apparatus, having a diameter of about 1 mm, and incubating the treated monocytes for a period of time sufficient to allow formation of functional

dendritic cells from the treated monocytes, as well as the step of incubating the treated monocytes with at least an antigen expressed on the surface of a disease effector agent) which is a species or sub-genus anticipating the claimed genus in the application being examined and, therefore, a patent to a genus would, necessarily, extend the rights of the species or sub-genus should the genus issue as a patent after the species or subgenus.

Conclusions

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339 or (571) 272-0776 after 01/13/2004.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, Gerald Leffers, Jr., Ph.D., may be reached at (703) 305-6232, or SPE, Remy Yucel, Ph.D., at (703) 305-1998.

Quang Nguyen, Ph.D.

GERRY LEFFERS
PRIMARY EXAMINER